Remarks

Claims 1-4, 17, 19-22, 27-116 and 120-150 are pending in the present application. Claims 35-41, 43-111, 122-129 and 139-147 are withdrawn from consideration. Claims 1-4, 17, 19-22, 27-34, 42, 112-116, 120-121, 130-138 and 148-150 are currently pending and under examination. Claims 1-4 and 17 are amended herein to provide proper antecedent basis for "monoclonal antibody." Claims 130-136 are amended herein to correct an inadvertent typographical error. No new matter is believed to be added by these amendments. In light of the following remarks, applicants respectfully request reconsideration of this application, entry of the new claims and allowance of the pending claims to issue.

Applicants appreciate having been granted the opportunity to interview this case on April 24, 2006 with Examiners Ouspenski and Gambel. During this interview, Dr. Richard Meagher described the hybridoma cells of the present invention, i.e. hybridoma cells that express the endogenous membrane form of a monoclonal antibody that is bound to the cell surface of the hybridoma cell. Also discussed at the interview is that the hybridoma cells can consistently and stably express the endogenous membrane form of a monoclonal antibody on their cell surface while maintaining their secretory abilities, thus solving a long existing problem in the art. By consistently presenting the endogenous membrane form of a monoclonal antibody on the cell surface of hybridoma cells, one of skill in the art can efficiently label and sort cells that produce a desired antibody, thus replacing current, tedious antibody screening and limit dilution procedures, with a rapid, high throughput selection process.

Also during the interview, the rejection of claims 1-4, 17, 19-22, 28-33, 42, 112-116, 120-121, 130-138 and 148-150 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Matsuuchi et al. in view of Maciak et al.was discussed. The following remarks specifically address this rejection.

Rejections Under 35 U.S.C. § 103(a)

A. The Office Action states that claims 1-4, 17, 19-22, 28-33, 42, 112-116, 120-121, 130-138 and 148-150 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Matsuuchi et al. in view of Maciak et al. In the paragraph bridging

pages three and four, the Office Action states that the discovery of a previously unknown molecular mechanism of immunoglobulin targeting to the cell surface, which Maciak et al. did not appreciate, does not disqualify the hybridoma cells taught by Maciak et al. as prior art. Furthermore, according to the Office Action, the teachings of Maciak et al. regarding the importance of obtaining maximal yields of antibodies from hybridoma cultures, and that the yield is positively correlated with the surface expression of the antibody, allegedly provide motivation for applying the teachings of Matsuuchi et al. to hybridoma cells, regardless of the underlying mechanisms.

Maciak et al. admit that they did not know if the immunoglobulin being detected on the hybridoma cell surface was the endogenous membrane form of the immunoglobulin. Thus, Maciak et al. cannot provide the requisite suggestion or motivation for one of skill in the art to apply the teachings of Matsuuchi et al. in order to produce hybridomas that can consistently express the endogenous membrane form of a monoclonal antibody on their cell surface.

Applicants reiterate that Maciak et al. did not know how immunoglobulin appeared on the cell surface of their hybridomas nor did Maciak et al. know for certain that the immunoglobulin being detected on the hybridoma cell surface was the membrane form of the immunoglobulin. As stated in column 4, lines 59-68, "[h]ybridomas also have Mabs of the same type and specificity associated, either integrally or passively, with the outer surface of the plasma membrane. At present, the exact mechanism by which these Mabs appear on the cell surface is unknown and in any event, the present invention does not reside in such mechanism." (Emphasis added). Applicants respectfully point out that obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. See MPEP 2141.02 V and *In re Rijckaert*, 9 F.2d 1531, 28 USPQd 1955 (Fed. Cir, 1993). Because the suggestion to combine or modify references must occur prior to an applicant's date of invention, an unknown inherency cannot supply this suggestion at the required time.

With regard to Matsuuchi et al., on page 5, the Office Action states that because Matsuuchi et al. teach that MB-1/Igα and Igβ are sufficient for cell surface expression even in the absence of other B cell specific components, this allegedly provides a clear

expectation of success for a skilled artisan in applying these teachings to other cell types, and in view of the motivation provided by Maciak et al. to hybridoma cells in particular. For the reasons stated above, Maciak et al. does not provide the requisite motivation for one of skill in the art to apply the teachings of Matsuuchi et al. to arrive at the present invention. Even if Maciak et al. provided motivation (which it does not), there would be no reasonable expectation of success for the skilled artisan to arrive at the present invention. As discussed during the interview, Matsuuchi et al. does not disclose or suggest any hybridoma, much less any hybridoma with increased amounts of the endogenous membrane form of a monoclonal antibody bound to the cell surface or any method of consistently producing a hybridoma with at least a two fold increase in the amount of the endogenous membrane form of a monoclonal antibody bound to the cell surface.

Furthermore, there is no indication in Matsuuchi et al. that the results obtained by transfecting a nucleic acid encoding Igα, a nucleic acid encoding Igβ and a cDNA encoding the membrane form of the μ heavy chain into AtT20 pituitary cells would result in an increase in the amount of monoclonal antibody bound to the surface of any other type of cell, much less a hybridoma cell. In fact, on page 3405, col. 2, Matsuuchi et al. states that "...MB-1 and Igβ were sufficient for surface expression of mIgM in nonlymphoid cells."(Emphasis added) Matsuuchi et al. further emphasizes this on page 3407 where it is stated that "[o]ur results demonstrate that MB-1 and Ig-β are the only B cell specific components required for cell surface expression of mIgM in a nonlymphoid cell line." (Emphasis added) Therefore, the Matsuuchi et al. reference says nothing about the requirements for cell surface expression of mIgM in a hybridoma cell, which is derived from a lymphoid line. Thus, it cannot be assumed that the results obtained in one cell will be equivalent to results obtained in another cell, particularly if the cells are of different lineages.

Furthermore, Matsuuchi et al. transfected a nonhybridoma cell with the nucleic acids encoding Igα and Igβ as well as a cDNA encoding the membrane form of the μ heavy chain. The increases observed by Matsuuchi et al. in a nonhybridoma cell that does not produce antibodies cannot be interpreted as equivalent to increases, if any, that one of skill in the art would see in an antibody producing cell, such as a hybridoma cell,

which is predisposed to secrete massive amounts of monoclonal antibody and, as will be discussed below, does not favor the production or presentation of the membrane form of a monoclonal antibody. Matsuuchi et al.'s results in no way disclose or suggest that the endogenous membrane form of a monoclonal antibody normally produced by a hybridoma cell (i.e., the membrane form of the monoclonal antibody with the specificity acquired from the B cell utilized to make the hybridoma cell) can be consistently presented on the membranes of hybridoma at levels that allow efficient labeling and selection of hybridoma cells. Also, by conducting experiments in nonhybridoma cells, there was no need for Matsuuchi et al. to overcome the predisposition of an antibody producing cell to secrete antibodies instead of presenting them on their membranes.

As discussed during the interview, Applicants overcame the hybridoma cell's predisposition to secrete monoclonal antibodies instead of presenting the membrane form of the monoclonal antibodies on their cell surface while still maintaining the hybridoma cell's ability to secrete monoclonal antibodies. Therefore, the hybridoma cells can consistently express the endogenous membrane form of a monoclonal antibody on their cell surface and can consistently secrete monoclonal antibodies, thus solving a long existing problem in the art. Furthermore, as pointed out by Dr. Meagher during the interview, these properties can be remarkably stable, thus overcoming the problems associated with instability of hybridomas obtained via traditional hybridoma production technology.

Also, as pointed out during the interview, it is well known in the art that hybridoma cells are the result of fusion between polyploid myeloma cells with diploid lymphocytes or B cells. As a result, genetic instability is associated with hybridoma cells. Therefore, there was no reasonable expectation that the transfection and expression results obtained in an AtT20 cell (endocrine cell utilized by Matsuuchi et al.) would be reproducible in any other cell, much less in a cell of different lineage, i.e. a hybridoma cell, with unpredictable genetic composition.

Furthermore, as discussed during the interview, at the time of the present invention, those in the field believed that the endogenous membrane form of the antibody was not expressed to any appreciable extent in a hybridoma cell. In support of this

assertion, Applicants provide herewith a Declaration pursuant to 37 C.F.R. §1.132 from Dr. Christine Milcarek, a shareholder of and consultant to Abeome Corporation, the licensee of the present application. In her Declaration, Dr. Milcarek declares that she is a Professor in the Department of Immunology at the University of Pittsburgh, School of Medicine, Pittsburgh, PA, with many years of experience in immunology. She further states that she is the senior author on Milcarek et al. ("Changes in Abundance of IgG 2a mRNA in the Nucleus and Cytoplasm of a Murine B-Lymphoma Before and After Fusion to a Myeloma Cell" *Mol. Immunol.* 33: 691-701 (1996). Therefore, she is very familiar with the methods and results described in this reference.

She further declares that this reference shows that after fusion of myeloma cells with a memory B cell line to produce AXJ hybrid cells, production of the secretory specific form of Ig heavy chain mRNA predominated over that of the membrane encoding form by 100:1 in the AXJ hybrid cells. This 100 fold increase in the ratio of secretory versus membrane forms of the immunoglobulin heavy chain in the hybrids was attributed to a 10 fold decrease in the production of the membrane form of the immunoglobulin by post-transcriptional RNA processing events whereas the overall amounts of nuclear RNA remain relatively constant between the hybrid cells and the B cells (see page 698, col. 2, last paragraph). Also contributing to the myeloma-like phenotype, i.e. secretory phenotype, of the hybrid cells is a decrease in the nuclear to cytoplasmic ratio for the secretory form of the γ2a immunoglobulin in the hybrid cells compared with the parent lymphoid cell line, with a smaller apparent change in the nuclear to cytoplasmic ratio for the γ2a membrane encoding form (see page 699, col. 2). She also declares that the numbers obtained for the membrane encoding form are very small and therefore difficult to quantify accurately, as evidenced by Figure 4 which shows that the membrane form of the immunoglobulin is barely detectable in AXJ hybrid cells.

She further declares that based on these results, at the time of the present invention, it was evident that the membrane form of the immunoglobulin is produced in small quantities in a lymphoid cell (e.g. a B cell) and that once fusion occurs with a myeloma cell, the amount of the membrane form of the immunoglobulin is further reduced. Therefore, she and others in the field believed that the endogenous membrane

form of the antibody was not expressed to any appreciable extent in a hybridoma cell. Since the endogenous membrane form of the antibody was not expressed to any appreciable extent, it could not be reasonably expected that one of skill in the art could present the membrane form of the immunoglobulin on the hybridoma cell surface via any means at consistently detectable levels.

Dr. Milcarek also declares that she is familiar with the work performed in Dr. Richard Meagher's laboratory on the production of hybridomas that reliably express the endogenous membrane form of a monoclonal antibody on their cell surface. This work is considered by herself and other colleagues in the field of immunology as a breakthrough in monoclonal antibody technology, since this is the first demonstration that the membrane form of a monoclonal antibody normally produced by a hybridoma cell (i.e., the endogenous membrane form of the monoclonal antibody with the specificity acquired from the B cell utilized to make the hybridoma cell) can be consistently presented on the membranes of hybridoma cells thus overcoming the difficulties and time constraints associated with traditional monoclonal antibody production technologies.

Thus, prior to Applicants' invention, there was no evidence that the hybridomas of the present invention could be obtained nor any suggestion of how to obtain them. As indicated by Dr. Christine Milcarek in her Declaration, since the endogenous membrane form of the antibody was not expressed to any appreciable extent, it could not be reasonably expected that one of skill in the art could present the membrane form of the immunoglobulin on the hybridoma cell surface via any means at consistently detectable levels. Prior to Applicants' invention, those in the field of monoclonal antibody technology were aware of no reasonable prospects to solve this problem. The evidence of record is consistent with this. Thus, the evidence of record is consistent with nonobviousness and supports the unexpected nature of the claimed hybridomas.

Therefore, based on the evidence described above, Applicants' invention provided a breakthrough in monoclonal antibody technology that would not have been obvious to one of skill in the art the time the application was filed. Thus, it would not have been obvious for one of skill in the art to combine Maciak et al. with Matsuuchi et al. to arrive at the hybridomas of the present invention. Therefore, Applicants believe that this

rejection as it pertains to claims 1-4, 17, 19-22, 28-33, 42, 112-116, 120-121, 130-138 and 148-150 has been overcome. Thus, Applicants respectfully request its withdrawal.

B. The Office Action states that claim 34 stands rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Matsuuchi et al., in view of Maciak et al. and further in view of Gossen et al. For the reasons discussed above, one of skill in the art would not have combined the teachings of Matsuuchi et al. with the teachings of Maciak et al. to arrive at the claimed invention. Therefore, it would not have been obvious to combine the teachings of Matsuuchi et al. with the teachings of Maciak et al. with the teachings of Gossen et al., directed to the use of inducible promoters to arrive at the claimed invention. Therefore, applicants believe this rejection has been overcome and respectfully request its withdrawal.

In view of the above remarks, reconsideration and allowance of the pending claims is believed to be warranted and such action is respectfully requested. The Examiner is encouraged to directly contact the undersigned if this might facilitate the prosecution of this application to issuance.

A Credit Card Payment Form PTO-2038 authorization payment in the amount of $905.00 ($395.00 for RCE fee, and $510.00 for extension of time fee – 3 months for small entity) and a Request for Extension of Time are included herewith. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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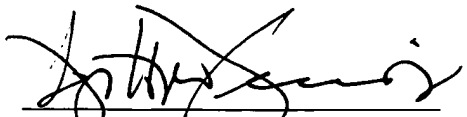

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